Clean Air Research Program Health and Exposure Summary and Abstracts

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Theme One: Health and Exposure

Theme Lead: Bob Devlin

By 1996, considerable evidence had accumulated suggesting that exposures to ambient particulate matter (PM) at or near the level of the then current National Ambient Air Quality Standard (NAAQS) were eliciting significant human health effects in the U.S. population. This evidence led to the promulgation of a new PM NAAQS in 1997, including a standard for PM smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$). The revised standard, coupled with continuing concerns and uncertainties regarding PM health effects, prompted Congress to augment the President's recommended U.S. Environmental Protection Agency (EPA) budget and charge EPA with accelerating investigations of the role of PM in air pollution-associated health outcomes and implementing health risk reductions via scientifically defensible regulatory actions. A comprehensive national research endeavor was initiated by EPA in 1998 and currently involves the coordinated efforts of intramural and EPA-funded extramural investigators, partners, and other Federal organizations that function within a scientific framework of research needs developed by an independent National Academy of Sciences National Research Council (NRC) committee of experts.

At the time of the last BOSC review, ORD's health effects and exposure research program was focused in the following areas: (1) understanding the relationship between community monitoring and individual exposures; (2) identification of PM components responsible for adverse health effects; (3) identification of the people most susceptible to PM; and (4) characterization of the mechanisms by which PM causes adverse health effects. While much uncertainty remains regarding PM-associated health effects, the four years of intensive research activity since that review have resulted in significant advances in health research. The ability of ultrafine particles to cause cardiovascular changes in toxicology studies is now well accepted, and a limited number of panel and epidemiology studies are now determining if exposure to these particles in real world situations is associated with mortality or morbidity. Toxicology and panel studies have also clearly shown that coarse particles can cause not only pulmonary but also cardiovascular effects in humans. Current studies are focusing on differences between coarse particles derived from urban and rural areas. Both epidemiology and toxicology studies done in the past 4 years have further defined the role played by specific components in PM toxicology, and efforts are underway to characterize health effects of specific sources (described in detail in Session 3 – Multipollutant research. New research has demonstrated the critical role played by vascular endothelial tissue in causing PM-induced cardiovascular effects, and shown that PM can translocate to the brain where it can cause both cellular and functional changes. Molecular approaches have strengthened the biological plausibility of PM health effects by defining cellular toxicity pathways that underlie those effects. Genetic technology has identified polymorphisms that are associated with increased responsiveness to air pollutants. Additional long term exposure studies have been reported and a large ten year effort is well under way to define progression of cardiovascular disease associated with air pollution. A new generation of exposure models is being developed to allow better exposure estimates in population-based studies. Recent studies have also revealed that ozone exposure can also be associated with increased mortality. The goal of these efforts, of course, is to provide health and exposure data appropriate to the review of the NAAQS and to ultimately assist the Agency in setting PM standards most protective of human health.

This session is intended to summarize and highlight the salient ORD-sponsored scientific advances in PM health and exposure since 2005. The session is framed around three themes:

1. What are the physical/chemical attributes of PM that are associated with adverse health effects?
2. How, and to what extent, does air pollution cause adverse health effects?
3. Who is susceptible to PM?

Theme 1. What are the Physical/Chemical Attributes of PM that are Associated with Adverse Health Effects.

The justification for the current PM NAAQS is primarily based on a large epidemiological database showing associations between ambient PM mass and excess mortality and morbidity. These associations are somewhat counter-intuitive, since PM pollution is a complex mixture of organic and inorganic constituents whose composition can vary widely depending on the time of year and geographical location. It exists over a wide range of sizes and geometries and contains several different classes of components comprised of hundreds of individual compounds. In order for the EPA to reduce the risk associated with PM exposure, it is critical to understand the contribution of various PM physical and chemical attributes (and the sources from which they arise) to the observed adverse health effects. Assessment of the toxic nature of PM must build upon a fundamental understanding that exposure to PM constitutes exposure to a complex mixture of particles of differing size and composition that may or may not be chemically or toxicologically altered by the various gaseous co-pollutants that coexist in an airshed. At the time of the last BOSC review, there was an intense effort to study health effects of different sized particles, and transition metals and reactive organic compounds present in PM. Today these areas remain a primary focus of ORD's research program but, as the posters described below demonstrate, substantial progress has been made in understanding health effects associated with PM size and components. Additional progress has been made in linking health effects with PM sources which is described more fully in **Session 3 (Multipollutant Research).**

Particle Size – Comparative Potency

Since PM is currently regulated on the basis of mass in specific size ranges, understanding the ability of different sized PM to cause health effects is critical in providing information that can be used to set a PM standard most protective of human health. Different size fractions of PM have different toxicological properties in terms of potency and adverse health effects. This difference in toxicity is due to different sources and thus chemical makeup that contributes to each size fraction, and differential deposition patterns which are based upon the aerodynamic properties of particles. The **poster presented by Gordon** describes recent efforts in which human CAPS studies have compared cardiopulmonary effects in humans exposed to ultrafine, fine, and coarse PM. In general, larger sized particles tended to produce inflammatory effects in the lung while the fine and ultrafine particles produce affected oxidative stress pathways and produced more systemic and cardiovascular effects. These observations have been confirmed in mice in which coarse particles from near and far roadway sites cause lung effects while the ultrafine particles affected cardiac function in an ex vivo perfusion model. In vitro toxicology has also been used to begin characterizing the mechanisms by which each size fraction elicits these changes

Particle Size – Ultrafine PM

The physical attributes of PM - size, surface area and number - are interrelated descriptive metrics of PM. These properties influence PM deposition, penetration, and persistence in the lung, as well as the potential for systemic transport and the inherent toxicity of the particle itself. Ultrafine particles (UFP) have a very high specific surface area, which can in principal make them more reactive chemically and biologically compared to larger-sized particles. Moreover, the larger surface area can function as a carrier for gaseous and semi-volatile co-pollutants. The chemical composition of ambient UFP includes elemental and organic carbon compounds, heavy metals and inorganic compounds, with the smaller UFP (<~20 nm) having higher amounts of organics. Furthermore, because of their small size, UFP have the potential to distribute to target sites outside the respiratory tract, including the cardiovascular system and the central nervous system (CNS).

While a few epidemiological studies show correlations between health outcomes and UFP, the bulk of the information regarding the toxic potential of this size fraction has derived from controlled animal or human exposure studies or in vitro studies. Four years ago there were a small but growing number of toxicology studies, many of them performed using artificially generated, that described the deposition pattern of UFP and presented the intriguing suggestion that at least some could cross the pulmonary barrier and enter the vascular system, where they might directly affect other organ systems. Because of their almost negligible mass, the current PM standards would not likely protect people from adverse health effects caused by UFP. Therefore it was deemed critical to better understand the health effects associated with UFP exposure. **The poster presented by Oberdorster** provides an update on studies that examine toxicological properties of ultrafine particles. It describes a small number of epidemiology studies that have begun to find associations between UFP exposure and mortality, as well as controlled exposure studies to UFP CAPS that show mild pulmonary inflammation, prothombotic, and cardiac changes. Convincing evidence is also presented that UFP can indeed travel to the brain and cause cellular and functional changes.

Particle Size - Coarse PM

Previously, less attention was paid to coarse PM ($PM_{2.5-10}$), primarily because the association between mortality and PM was much stronger for fine PM ($PM_{2.5}$). Coarse PM originates from abrasive practices such as milling and sand-blasting, re-dispersion of crustal and biogenic material, and natural processes like sea spray and pollen release. It makes up 30 – 50% of PM mass depending on the geographical local. Elemental analysis shows enrichment in crustal metals such as aluminum silicates and lower amounts of combustion byproducts such as organic and elemental carbon and sulfates. Coarse and fine particles have different physical characteristics and lung deposition patterns, and likely have different potency, toxicity, and biologic effects. Moreover, coarse PM from different locales (urban versus rural) has different chemical components. Recent questions about health effects associated with coarse PM and the need for a dual urban/rural standard have elevated the issue of coarse PM health effects to a high priority for the Office of Air and Radiation (OAR

The poster presented by Carraway describes ORD's research on health effects associated with coarse PM, with a focus on CAPs studies that show cardiopulmonary effects in humans, and mechanistic studies in cells and mice that attempt to link health effects with specific coarse PM components. The results also describe physiological and health-related comparisions of coarse PM from urban and rural areas.

Particle Composition – Metals and Organics

At the time of the last BOSC review, most epidemiological work focused on mass based causation, since there were few sites which provided daily speciation data. The increased availability of this information has led to newer epidemiology studies which associate risk of mortality/morbidity with PM components. These studies are described in the **poster presented by Dominici in Session 3**.

At that time, a significant portion of ORD's toxicology research on PM components focused on studies using emission particles enriched for metals such as ROFA, or soluble metal salts. These studies have evolved to include real world particles and an increased emphasis on other components as well such as organic PM constituents. The **poster presented by Kodavanti** describes these efforts. A major initiative is the HEI sponsored National Particle Component Toxicity Initiative (NPACT), an integrated epidemiology and toxicology study which will investigate both short and long term effects of PM components. Recent studies linking zinc and nickel with adverse health effects are also presented, as are studies examining the contribution of redox and electrophilic activities associated with polar organic materials. Organic components of PM have not been as extensively studied as metals or particle size, with the exception of those components emitted in diesel exhaust, primarily because of the difficulty in accurately characterizing in detail the classes of organic compounds present in ambient PM samples. The **poster presented by Cho** describes recent studies which have examined cardiopulmonary effects associated with organic components.

What Remains to Be Done?

Although numerous studies in the past four years have examined a wide range of PM chemical and size characteristics, the results of these studies have not always been consistent. Furthermore, they have not yet been able to narrow down the list of potential PM properties to bring greater focus to research on PM components. For example, there are now numerous toxicology studies which suggest that ultrafine particles may be particularly toxic, but many of them were done at very high concentrations. Epidemiology studies are needed to determine if adverse health effects are associated with exposure to "real world" ultrafine particles. Continuation of research using statistical approaches to link health effects with specific components or physical properties in ambient PM will be important in future studies, not only because of their potential to identify relevant components, but also because of their potential to link health effects with specific sources of PM. Additional mechanistic studies are also critical; if several components exert their effects by the same or similar mechanisms (such as oxidative stress), this information would have important implications for control strategies. It will also be important to conduct toxicology studies in conjunction with these epidemiology studies. When information from toxicology, epidemiology, and panel studies conducted in the same areas can be integrated, it will offer a new opportunity to investigate coherence across disciplines. When interwoven, these approaches should provide considerable insight into the components and sources that can be linked to PM-associated heath outcomes.

Theme 2. How and to What Extent does Air Pollution Cause Adverse Health Effects?

The current PM standard rests primarily on a large and coherent epidemiological database of significant associations between ambient air PM concentrations and excess mortality and morbidity. At the time of the last BOSC review, there were a number of human and animal toxicology studies underway that addressed the biological plausibility of how exposure to very

small levels of PM (less than 1/20th of what would be inhaled from a single cigarette) can lead to death within hours. In addition, studies had begun to describe the cellular or molecular mechanisms that underlie the presumed pathophysiological processes responsible for adverse health effects, especially those associated with long term exposure to PM. During the past four years many of these studies have come to fruition and significant advances have been made in characterizing relevant physiological, cellular, and molecular pathways, as well as focusing attention on newer issues such as the critical role played by the vascular tissue, PM effects on the nervous system, and mortality associated with ozone exposure.

Long Term Exposure and Increased Atherosclerosis

The current annual $PM_{2.5}$ standard is based on a relatively small number of cohort studies of long-term exposure, notably the Harvard Six Cities Study and the American Cancer Society Study, which found significant associations between annual cardiopulmonary mortality rates and long-term average $PM_{2.5}$ concentrations. While the results of these studies were compelling, they were limited by a lack of detailed health outcome data, individual-level risk factor information and characterization of exposure beyond a metropolitan area average concentration. Since 2006, two additional cohort studies have added to the epidemiologic database regarding the relationship between long-term exposure to PM and CVD: the Women's Health Initiative-OS and the Nurses' Health Study. These studies also found significant increased risk of CVD- and CHD-related death associated with increasing PM exposure.

In 2004, the EPA funded a large-scale prospective cohort study of air pollution and CVD, the MESA Air study. This 10-year, multi-city, multi-ethnic study combines state-of-the-art cardiovascular epidemiology with state-of-art exposure assessment, and is intended to provide precise estimates of the health risks associated with long-term exposure to PM. **The poster presented by Kaufman** summarizes the Women's Health Initiative-OS and the Nurse's Health Study, as well as recent studies in which animals were exposed to fine + ultrafine CAPS for 6 months. However the main focus of this poster is a description of the MESA Air Study and the progress that has been made since its inception.

PM Effects on the Vascular System

At the time of the last BOSC review, most PM clinical and toxicology studies were dominated by end points which examined changes in heart rate variability and soluble vascular markers (e.g. CRP or clotting/coagulation factors). There were a few intriguing studies which suggested that blood vessels may also be targets for PM effects. The vascular system coordinates systemic hemodynamics and tissue perfusion, vasomotor tone, vascular integrity, coagulation, thrombosis, and response to injury. A dysfunctional vascular endothelium is the earliest manifestation of atherosclerotic vascular disease, the major cause of myocardial infarction and cardiovascular mortality. Intact endothelial function prevents vascular inflammation/oxidative stress and the development of atherosclerosis and hypertension. Since that review, there has been an increased emphasis on understanding how PM can cause vascular dysfunction and associated physiological responses. The **poster presented by Brook** describes these advances. The poster describes studies in which PM exposure has been shown to impair aspects of systemic and pulmonary vascular function including vasomotor tone. These studies show that PM inhalation is capable of adversely affecting the systemic vasculature by 2 broad pathways. 1) Release of inflammatory mediators (activated white blood cells or platelets, cytokines) and/or hemodynamically-active molecules (endothelins) from lung-based cells into the systemic circulation, and 2) autonomic nervous system imbalance favoring sympathetic activity to the vasculature via PM-induced activation of pulmonary receptors or neural reflexes. Subsequent biological responses include an increase in blood pressure, vasoconstriction, impaired endothelial-dependent vasodilatation,

blunted myocardial perfusion, vascular inflammation and oxidative stress, along with altered matrix metalloproteinase activity. Chronic exposure studies also demonstrate the capacity of PM to accelerate the progression of atherosclerosis. These experiments corroborate that vascular dysfunction is likely a pivotal biological mechanism explaining the increase in risk for cardiovascular morbidity and mortality due to PM exposure.

PM and Molecular Mechanisms

In addition to understanding biological mechanisms at an organ or tissue level, complete understanding of how PM causes adverse health effects requires knowledge of the molecular, biochemical, and cellular mechanisms which control the pathophysiological responses to PM. **The poster presented by Samet** exemplifies this type of cutting-edge research, which seeks to understand what happens from the time a particle touches the outer surface of a cell until a battery of genes is activated which will trigger a cascade of events leading to an adverse health response. This approach can also lead to the identification of mechanisms that may be responsible for several pathophysiological responses, as well as characterize different PM components by how they damage tissues. Although several examples of this approach could have been chosen, this poster focuses on a specific mechanism as an illustration of the overall approach. Many studies suggest that the effects of PM involve inflammatory responses in the cardiovascular and respiratory systems. Inflammation is known to be mediated by inflammatory proteins whose expression is under the control of specific signal transduction pathways. These signaling cascades are regulated by the opposing activities of kinases and phosphatases which modulate the levels of phosphoproteins - proteins phosphorylated on tyrosine, serine and threonine containing amino acids. These phosphoproteins include signaling intermediates such as transcription factors as well as kinases and phosphatases themselves, which may be affected by PM exposure. This poster describes studies which characterize the role of these signaling pathways in transducing a signal from PM or a PM component to downstream genes.

PM and Oxidative Stress

A significant advance since the last BOSC review has been a better understanding of the link between oxidative stress and the ability of PM to induce pro-inflammatory effects in the respiratory and cardiovascular tissues. **The poster presented by Cho** presents recent work focused on oxidative stress as an underlying mechanism that might explain pulmonary, vascular, and cardiac effects caused by PM. It also shows that two very different PM components, metals and organic compounds, may both cause adverse effects by inducing oxidative stress. It describes cellular and in vivo assays that have been used to quantify oxidative stress and thiol alkylation induced by PM and its components.

The hope is that the assays can be used as measures of biologically relevant exposure in epidemiological studies, and as air quality indicators that respond to the mixture of multiple pollutants in ambient air with applications to the design and evaluation regulatory air pollution control programs.

PM and the Nervous System

At the time of the last BOSC review there was a single study suggesting that MnO_2 ultrafine particles could translocate to the brain via the olfactory nerve. This possibility stimulated a number of additional studies which are described in the **poster presented by Kleinman** as well as a portion of the **poster presented by Oberdorster**. They leave little doubt that PM exposure can affect the nervous system by causing cellular and biochemical changes in the brain, as well as potentially altering downstream autonomic nervous system function which regulates a number of cardiac and vascular pathways. Work is presented indicating that neurons from the substantia

nigral nucleus compacta are significantly reduced in Apo E-/- mice exposed subchronically to fine plus ultrafine (CAPs). Other studies show that PM can upregulate pathways associated with inflammation in the brains of mice exposed to PM.

Ozone Mortality

At the time of the last BOSC review, epidemiological studies that included ozone were based on short-term exposure (effects from ozone levels on the same and previous few days) in single cities. Findings from these earlier studies were inconclusive with some studies identifying an association whereas others did not. However, a recent wave of studies have added substantial evidence regarding the association between exposure to tropospheric ozone and risk of human mortality. These studies have included a range of study designs including meta-analysis, case-crossover, and multi-city time-series studies to examine the association between short-term exposure to ozone and risk of mortality, as well as a study to examine the mortality risk from long-term exposure to ozone through a cohort design. This work is described in the **poster presented by Bell**. The poster summarizes the use of meta-analysis and multi-city approaches, and identifies potentially susceptible populations. It also describes work to identify threshold effects as well as an ACS study looking at the association between long term ozone exposure and mortality.

Improved Exposure Characterization

Most epidemiology studies rely on central-site ambient monitors to characterize PM exposures. This does not account for the spatial–heterogeneity of ambient PM patterns, the temporal variability in ambient concentrations, nor the influence of infiltration and indoor sources. Central-site monitoring becomes even more problematic for certain PM components (e.g., metals) or size fractions (e.g, coarse, ultrafine) that exhibit significant spatial-heterogeneity. The **poster presented by Baxter** describes recent approaches to estimating ambient concentrations, source apportionment, a better understanding of the personal-ambient relationship, and personal exposure modeling. Techniques such as the Community Multi-Scale Air Quality (CMAQ) model and land-use regression modeling can enhance estimates of ambient PM concentrations. Development of both personal (EMI) and population based (SHEDS-PM) exposure models is also described. It is anticipated that improved models of ambient concentrations can be used in the reanalysis of existing PM health studies leading to more precise and potentially larger health effect estimates.

What Remains to Be Done

The work captured in the posters described above shows that considerable progress has been made in understanding some of the pathophysiological mechanisms that underlie PM effects. However, research is still far from being able to clearly explain the pathways by which very small concentrations of inhaled ambient PM can produce the cardiovascular and pulmonary changes that can contribute to increased mortality/morbidity. Many of these studies have yet to be repeated enough to instill confidence in their results. Furthermore, as new susceptible populations (e.g. pregnant women) and new target organ systems (e.g. the nervous system) are identified, additional mechanistic research will be necessary to fully explain the effects of PM in humans. Much like the original PM epidemiology studies, the recent epidemiology studies reporting associations between ozone and mortality should be buttressed by clinical and toxicology studies which provide biologic plausibility as to how ozone can cause acute mortality. It will also be important to determine if PM and ozone causes adverse health effects by similar mechanisms. Finally, toxicological evaluation of air pollutants is poised to take advantage of the current revolution in systems biology approaches (NAS report entitled “Toxicity Testing in the

21st Century") which use computational models and laboratory data from toxicity pathway studies - the cellular response pathways that can result in adverse health effects when sufficiently perturbed - to describe and understand biologic systems as a whole and how they operate. These new tests have the potential to link changes at the molecular level with functional changes in humans, helping EPA better predict how air pollutant exposures do or do not lead to certain health effects and how they affect sensitive populations.

Theme 3. Who Is Susceptible to PM?

An understanding of susceptibility is critical to achieving the public health protection called for by the 1990 Amendments of the Clean Air Act, which extended protection against adverse health effects beyond the general population to especially susceptible subpopulations. The population as a whole is heterogeneous in its susceptibility to particles. However, diverse characteristics that may increase susceptibility to adverse health effects from inhaled PM include age (infants and older adults), the presence of underlying disease (chronic heart and lung diseases), altered deposition and clearance (morphological and physiological changes in the respiratory tract), activities that increase lung dose (e.g. physical work). Initial time-series epidemiological studies associating mortality and hospital admissions with daily ambient PM concentrations indicated that elderly people with cardiopulmonary disease (e.g. COPD, severe cardiovascular disease) were at the greatest risk.

PM and Pre-existing Cardiovascular Disease

At the time of the last BOSC review, an impressive array of epidemiology, clinical and toxicological studies left no doubt that people with pre-existing cardiovascular disease are at increased risk from exposure to PM. Several mechanisms of PM-induced cardiac dysfunction in humans were postulated including autonomic modulation, direct effects of PM constituents on ion channels, myocardial ischemia, and vascular dysfunction related to systemic inflammation. Recent epidemiological, clinical, and toxicological studies have increased our understanding of how pre-existing CV disease confers enhanced sensitivity to the effects of PM inhalation. The **poster presented by Farraj** describes studies which have begun to elucidate the underlying mechanisms by which PM affects people with cardiovascular disease. It characterizes autonomic, inflammatory, antioxidant and coagulation pathways which may be driving these effects. Future efforts will focus on the role of specific components and sources

PM and Diabetes

The U.S. is experiencing an epidemic of type 2 diabetes and its associated conditions, obesity and metabolic syndrome. It is estimated that 26% of U.S. adults have abnormal fasting glucose levels, or pre-diabetes. Many of these individuals will go on to develop type II diabetes. At the time of the last BOSC review, epidemiology studies suggested that diabetics have an increased mortality risk from exposure to particulate matter (PM), and double the risk of non-diabetics for a cardiovascular hospitalization related to PM exposure. It appears that diabetics have an enhanced risk factor for PM over and above the cardiovascular disease that many of them develop as their disease progresses. While mechanistic pathways for the cardiovascular effects of PM have been proposed and are being investigated, the role of diabetes in mediating susceptibility to these effects is not clear. However, diabetes pathophysiology includes features considered to be important in the health effects of PM: oxidative stress, systemic inflammation, endothelial dysfunction, hypercoagulability, and increased atherosclerosis. The **poster presented by Frampton** describes advances in our understanding of the role of diabetes, and of

related conditions such as obesity and the metabolic syndrome, in PM health effects. Epidemiology and panel studies continue to find associations between PM exposure and cardiovascular effects in diabetics, and some studies suggest that PM exposure further reduces the already impaired vascular function in diabetics. Animal models of diabetes, obesity, and insulin resistance have been used to define cardiovascular changes associated with exposure to PM. These advances have increased our confidence that diabetics are more responsive to PM as well as delineated some of the pathways responsible for this responsiveness.

PM and Asthma

At the time of the last BOSC review, it was accepted that air pollution is a significant cause asthma exacerbation. Studies have shown convincingly that during episodes of air pollution, emergency room visits and medication use in asthmatics increase. Air pollution is likely second only to viral respiratory tract infections as a precipitating factor in acute asthmatic events, rescue medication use, ER visits and hospitalizations. However, while earlier epidemiological studies demonstrate that PM contributes to exacerbation of asthma, the degree to which PM influences disease progression, and the potential for PM to contribute to pathogenesis of asthma were not well understood. It was also unclear if specific exposure scenarios (e.g. near road) or specific components of PM such as bioaerosols found in coarse particles are more likely to cause asthma exacerbation. The **poster presented by Peden** describes newer studies that characterize PM components and mechanisms by which PM may cause asthma exacerbation, as well as a single study suggesting that air pollution may actually contribute to the onset of asthma in children. It also describes panel and clinical studies that demonstrate cardiovascular effects in mild asthmatics, even in the absence of pulmonary effects.

PM and Genes

Medical research continues to identify genetic polymorphisms that are associated with increased susceptibility to developing a disease. Earlier research had demonstrated a wide heterogeneity in response to air pollutants among ostensibly healthy individuals, suggesting that factors other than pre-existing disease, age, etc. might be contributing to the enhanced responsiveness. However, when these studies were intially done, the genetic tools were not available to identify these factors. The recent revolution in "omics" technology has provided the tools that can be used to address this question and it is critical to be able to identify genetic alleles present in a significant proportion of the population which could confer added susceptibility to air pollutants on individuals carrying those alleles. Since the last BOSC review, a growing number of alleles have been identified that appear to confer added susceptibility to PM. These studies are described in the **poster presented by Schwartz**. In addition to identifying potentially susceptible groups, this research effort is also able to delineate specific mechanisms by which PM might be causing adverse health effects. For example, studies have shown that polymorphisms that affect response to oxidants and metal-rich particles confer added responsiveness to both humans and animals. Other studies have associated polymorphisms related to endothelial cell function with added responsiveness. Very recent ORD research has also shown that epigenetic processes such as DNA methylation can contribute to PM susceptibility.

What Remains to Be Done?

There is growing recognition that the subpopulations who are most susceptible to air pollution and the factors related to increased health risks are more numerous and diverse than once thought. Although substantial progress continues to be made in identifying susceptible populations such as diabetics, there is still much to be learned about the underlying risk factors

that make people with pre-existing disease susceptible to air pollution. Additionally, a better understanding of the role of genetic and epigenetic factors is critical, since they may impact large segments of the population who would never suspect they are susceptible to air pollutants. Thus, while the first step is to identify susceptible groups within the general population for inclusion into the overall risk assessment paradigm, characterizing the risk factors that underlie susceptibility and the mechanisms which underlie increased responsiveness may be the most fruitful in the long run by virtue of their predictive power. It is also important to develop new biomarkers of susceptibility using cutting edge molecular "omics" approaches and identifying potential intervention strategies to better protect susceptible populations from air pollution. Finally, almost nothing is known about whether chronic exposure to air pollution plays a role in the development or progression of cardiopulmonary disease.

Conclusions

At the time of the last BOSC review the PM NAAQS rested primarily on a robust set of time series epidemiology studies which, though they were coherent with one another and compelling, were nonetheless viewed as insufficient by some to warrant strengthening the PM standard. The work shown in the posters in this session clearly demonstrate that PM research in the areas of Health and Exposure has made tremendous progress since 2005. Although there is still work to be done, these results have already played a key role in the process by the EPA recommends Air Quality standards. **The poster presented by Stanek** describes how ORD research is used to assist the ORD research and scientific review, which are integral to the NAAQS process. The research of ORD's scientists, grantees, and research partners contributes substantially to the scientific literature from which the PM ISA is compiled and is key to the science foundation for NAAQS recommendations in the OAR Staff Paper. For example, ORD health-associated publications comprised approximately 40% of the referenced publications in the latest draft PM Staff Paper. Also, scientists throughout ORD (both intramural and extramural) commit many hours to writing and reviewing key sections of the PM ISA. Similarly, they provide important review and feedback on the Staff Paper. In addition to providing peer-reviewed publications that are integral to the PM standard-setting process, ORD researchers also have other scientific interactions with OAR, some of which are described in t**he poster presented by Hasset-Sipple.** Additionally, the Office of Air and Radiation has used ORD sponsored research in various ways to better inform the public about the threat of air pollution and protective measures that can be taken. Some of these efforts are described in the **poster presented by Stone**.

Poster # LTG 1-01

Do Different Size Fractions of PM Cause Different Health Effects?

Presenter: Terry Gordon, NYU School of Medicine, Tuxedo, NY

Poster Summary: An increasing database suggests that specific physico-chemical properties of ambient PM can be linked to the adverse cardiopulmonary effects of PM. Different size fractions of PM have different toxicological properties in terms of potency and adverse health effects. This is due to both the different sources and thus the chemical makeup of the different size fractions of PM, and differential deposition patterns which are based upon the aerodynamic properties of particles. Particulate air pollution is broadly characterized and currently regulated in two principal size fractions; PM_{10} and $PM_{2.5}$. Airborne coarse PM ($PM_{10-2.5}$) originates from mechanical abrasion such as milling and sand-blasting, windblown re-dispersion of crustal and biogenic material, and natural processes such as sea spray and pollen release. The coarse fraction makes up more than 50% of the PM mass in the West Coast and between 30 and 40% in the Central U.S. and East Coast. Elemental analysis shows enrichment of metals such as aluminum silicates with lower amounts of combustion byproducts such as organic and elemental carbon and sulfates. Because of its aerodynamic size, coarse PM deposits in the large airways and mostly impacts the thoracic region of the lung. EPA-funded projects are at the forefront of research and epidemiology, animal toxicology, and *in vitro* studies and have made several critical determinations used in ongoing PM risk assessment and management. In particular, it has been shown that the coarse fraction of ambient PM, on a mass concentration basis, produces more pulmonary inflammatory responses and cytotoxicity than other size fractions in animals and cell experiments. For example, EPA's PM Centers have collaborated to compare the toxicity of coarse, fine, and ultrafine particles collected throughout the U.S. *In vitro* and *in vivo* results have demonstrated that coarse particles can be more toxic, on a mass concentration basis, than fine and ultrafine particles. Animal exposure studies in California, however, have found little difference in the ability of coarse vs. fine particles to cause lung injury and inflammation in mice treated with PM via intratracheal instillation. In other studies however, inhalation of concentrated ambient PM produced particle size-dependent differences in the cardiopulmonary response of mice. In particular, ultrafine PM produced greater gene expression changes in heart tissue than did coarse or fine PM. The animal and *in vitro* studies contrast recent epidemiology work which has found that fine particles may predominate in time series studies of PM's adverse cardiopulmonary effects. A key issue in the risk assessement of coarse PM is the different composition of urban vs. rural particles. EPA investigators have directly examined the role of biologic components of coarse PM by measuring cellular and cytokine indices of inflammation in human volunteers. This clinical study demonstrated significant effects of biologic components in coarse particles and suggested a role for bacterial agents in the immunomodulatory effects of PM, which may be more common in rural settings. The purpose of this poster is to provide illustrative data that contrast and quantify the adverse health effects of coarse, fine and ultrafine PM and determine the responsible components/sources.

Impact and Outcomes: The results of these studies directly feed into Integrated Science and Risk Exposure Assessments and standard setting for PM. In addition, the information is used by the Office of Air and Radiation and the Office of Transportation and Air Quality for hazard identification and risk and benefits assessment purposes. The fact that coarse PM is more prevalent in the West Coast has implications for the development of regional standards versus attainment of the national standard. Because coarse PM is predominantly an outdoor air pollution problem, it may disproportionately affect children and others who spend more time outdoors. Furthermore, coarse PM tends to deposit in the conducting airways of the respiratory tract and therefore people with airway diseases such as asthma may be especially susceptible to its effects.

Future Directions: The relationship between particle size and composition in PM's adverse health effects is complex. Although a significant amount of research has addressed the role of particle size in causing toxic effects, expanded research is needed to distinguish the roles of time (e.g., daily and seasonal changes) and spatial (e.g., Eastern vs. Western U.S.; height of sampling monitors) variabilities in particle composition across coarse, fine, and ultrafine particle sizes.

Relevant Publications

Alexis, N.E., Lay, J.C., Zeman, K., Bennett, W.E., Peden, D.B., Soukup, J.M., Devlin, R.B., Becker, S., 2006. Biological material on inhaled coarse fraction particulate matter activates airway phagocytes in vivo in healthy volunteers, *J Allergy Clin. Immunol.* 117, pp. 1396-1403.

Cho, SH., Tong, H., McGee, J., Baldauf, R., & Gilmour, MI. Comparative toxicity of size-fractionated airborne particulate matter collected at different distances from an urban highway (submitted to Env Health Perspect).

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Poster # LTG 1-02

What are the effects of ultrafine particles (UFP)?

Presenter: Günter Oberdörster, University of Rochester

Poster Summary: Data from epidemiological, clinical and toxicological *in vitro* and *in vivo* studies have shown that UFP have significant potential to induce local effects (at the portal of entry, the respiratory tract) as well as secondary organs including the cardiovascular system, and the central nervous system (CNS). Mechanisms underlying the extrapulmonary effects have been based on 3 hypotheses: 1. Locally induced target cell activation and inflammation at the site of deposition leads to a systemic acute phase response via released mediators. 2. Inhaled UFPs translocate across epithelial and neuronal pathways and distribute to and cause effects in secondary organs. 3. UFPs activate sensory nerves in the conducting airways of the tracheobronchial and the naso-oro-pharyngeal regions affecting the autonomous nervous system. Associations have been reported between ambient UFP levels (measured as particle numbers rather than mass) and increased mortality and morbidity. For example, a study by Breitner *et al*. (2009) reported a significant association between locally-generated UFP number concentrations in the city of Erfurt, Germany and mortality based on data collected between 1991 and 2002. The cumulative 6-day RR was significant for UFP, but not for $PM_{2.5}$ or PM_{10}. The smaller UFP (10-30 nm) showed larger associations. With increasing control measures that decreased UFP concentrations, the associated RR decreased as well. Delfino *et al*. (2009) were able to separate measurements between $PM_{2.5}$ and quasi UFP (<250 nm) in the immediate outdoor community of retired elderly persons and found a stronger association between blood markers of inflammation (IL-6; sTNF RII) for particle number and $PM_{0.25}$ than for $PM_{2.5}$. Persons not taking statins had an even stronger association with UFP. Other data provided evidence for direct effects on the cardiovascular system and the CNS. These include intravenous injection studies of different types of ambient UFP into normal, hypertensive or aged rats resulting in premature heartbeats; in isolated perfused hearts of these rats, positive and negative inotropic effects and decreased coronary blood flow was observed (Simkovich *et al*. 2008; Wold *et al*. 2006; Hwang *et al*. 2008). Inflammatory CNS effects and neurodegenerative effects were observed in mice following exposures to ultrafine/fine traffic aerosols (Campbell *et al*. 2005; Veronesi *et al.* 2005); ultrafine Mn-oxide (~30 nm) inhalation for 12 day induced a large inflammatory response in the olfactory bulb of rats as a consequence of nose to CNS translocation of these UFP. CNS effects were also observed in EEG recordings of diesel exhaust exposed subjects (Crüts *et al.* 2008); and a decrease in verbal and non-verbal intelligence and memory in children correlated with exposure to traffic-related aerosols (Suglia *et al.* 2008). Cardio-vascular effects of traffic-related UFP exposures were reported in on-road rat studies (Elder *et al.* 2007), controlled clinical studies (Frampton *et al*. 2006), and epidemiological studies (Peters *et al*. 2006; Rückerl *et al*. 2006, 2007).

Impacts and Outcomes: These studies are representative for a mounting number of animal, clinical and epidemiological studies showing significant health effects of inhaled ultrafine particles in general and from traffic-related sources in particular. There is an obvious need to determine the contribution of direct *vs*. indirect mechanistic events of extrapulmonary effects of inhaled UFP. Such knowledge is important to EPA with regard to considering regulations aimed at reducing anthropogenic emissions of UFP from specific sources. Especially the impact on susceptible parts of the population needs to be considered.

Future Directions: Identifying physico-chemical characteristics of UFP from different sources and determining their reactivities/effects is of high priority to better assist the EPA in deciding whether a number based standard might be necessary. Results from long-term exposures are specifically needed as are studies on combined effects of UFP with other air pollutants.

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Poster # LTG 1-03

What are the Health Effects of Coarse Particles?

Presenter: Martha Sue Carraway, US EPA Office of Research and Development

Poster Summary: Epidemiological and toxicological evidence indicate that exposure to fine air pollution particles ($PM_{2.5}$), which are primarily derived from combustion processes, causes increased morbidity and mortality. Information is less certain about adverse health effects associated with exposure to coarse particles, which are typically derived from soil or abrasive mechanical processes in transportation, agriculture and industry, and also contain biogenic materials. Coarse and fine PM have different physical characteristics and lung deposition patterns, and likely have different potency, toxicity, and biologic effects. Research is needed to define the relative mass, chemical composition, source characteristics and exposure estimates of coarse PM in different locations, and how these affect health. Such studies are necessary to determine whether coarse PM causes significant adverse health effects, and if coarse particles derived from urban and rural sources are equally toxic. A panel study performed in adult asthmatics showed that small temporal increases in ambient coarse PM affected important cardiopulmonary and lipid parameters without measurable effects on lung function. Another panel study found that asthmatic children with muted expression of CD14 on circulating neutrophils were more susceptible to the detrimental effects of PM on pulmonary function, especially coarse PM. In contrast, children with measurable neutrophil CD14 expression were much less susceptible to the effects of PM on pulmonary function. Controlled human exposure studies in normal healthy volunteers exposed to coarse CAPS exhibit mild pulmonary inflammation, pro-coagulant changes in plasma, and altered cardiac repolarization. Current studies are examining health effects of coarse CAPS in asthmatics and assessing health effects associated with urban and rural coarse CAPS in hypertensive and non-hypertensive individuals. A mechanistic study in human volunteers showed that the heat labile biological components of coarse PM mediate macrophage TNF-alpha production, cell surface marker responses, and phagocytosis, but are not required to evoke neutrophilic inflammation. These data suggest that coarse PM activates monocytic cells and may play a role in exacerbation of immune –mediated diseases such as allergic asthma.

Impact and Outcomes: Results of these studies will strengthen the scientific basis for the coarse PM NAAQS by providing important information to OAR as to whether coarse PM causes significant adverse health effects, and whether these are similar or different with fine and ultrafine PM. The results will also reduce uncertainties as to the need for a dual urban and rural coarse standard.

Future Directions: Further research is needed to determine the type and severity of health outcomes associated with coarse PM, and whether specific populations such as asthmatics are more susceptible to health effects. Characteristics of coarse PM need to be correlated with differences in health outcomes. Epidemiological studies are planned to assess and compare health outcomes in rural and urban locations in Colorado, and will compare daily coarse PM levels to specific measures of morbidity. Physiological effects of coarse and rural coarse particles will be compared in experimental animals and in controlled exposures of human volunteers.

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Poster # LTG 1-04

What Is the Influence of Different Components on the Health Effects Of PM?

Presenter: Urmila P. Kodavanti, US EPA Office of Research and Development

Poster Summary: Respirable ambient PM is composed of diverse elemental and organic components in various chemical forms, often contaminated with biological materials. Remarkable dynamic, spatial and temporal variations have been noted in the composition and surface chemistry of atmospheric PM. It is important to identify those PM components responsible for adverse health effects. This poster will focus on assessing the health effects associated with metals and organics in spatially and temporally different ambient PM. ***Research goals are:*** 1) to identify causative components of ambient PM variably enriched by different industrial and traffic sources, and 2) to understand the contribution of each component and specific mechanistic differences in pulmonary and extra pulmonary health outcomes. ***Major findings include:*** 1) PM dominated by vehicular and industrial emissions is enriched with both metals and organics and the redox activity of PM enriched by organic polycyclic hydrocarbons is much greater than metals or anions. Changes in circulating biomarkers of cardiovascular effects are best associated with elemental and organic content of PM. 2) In ambient PM samples where nickel and vanadium are detected; these metals show the strongest association with mortality. 3) Animal CAPS inhalation studies and intratracheal instillation experiments show that nickel, zinc and copper are most toxic to the lung and heart. 4) PM-associated soluble and acid leachable metals translocate to the circulation and extrapulmonary organs, disturb essential metal homeostasis, and produce direct cardiac effects. 5) Zinc and diesel exhaust effects on the heart are distinct in terms of specific genes being up or down regulated in rats. 6) Epidemiological associations, animal toxicological studies involving concentrated ambient particles, individual metals or organic-rich diesel exhaust, and in vitro redox activity studies are coherent and support the role of these components in cardiopulmonary mortality.

Impacts and Outcomes: 1) Identification of causative components of ambient PM is required for the Program Office to recognize potential contributing sources such that regulatory decision on reducing harmful emissions can be supported by scientific evidence. The data on health effects of components also provide guidance for improved emission technologies that produce less harmful pollution. EPA supported studies provide evidence that PM-associated metals and organics originating from industrial and vehicular emissions are likely responsible for pulmonary and cardiovascular effects associated in humans. Since the effects induced by metal-rich PM and organic-rich diesel exhaust may involve distinct mechanisms, a number of different health effects and biomarkers need to be considered.

Future Directions: 1) Conduct human and animal CAPS studies in which statistical methodology is used to determine the contribution of specific components to cardiopulmonary effects. 2) Perform controlled acute and chronic animal studies in parallel using compositionally different PM to identify mechanistic differences in cardiovascular health effects. 4) Determine the role of surface chemistry and soluble components using freshly generated versus photochemically aged source emissions and ambient PM generated in differentially controlled environmental conditions and using potential air contaminants.

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Poster # LTG 1-05

Does Long-Term Exposure to PM Cause Atherosclerosis?

Presenter: Joel Kaufman, University of Washington

Poster Summary: In 2006, the EPA conducted a review of the PM standard, which resulted in a revision of the 24-hr $PM_{2.5}$ standard developed during the 1997 NAAQS process, but retained the annual standard. The annual standard was based primarily on cohort studies of long-term exposure, the Harvard Six Cities Study and the American Cancer Society Study, which found significant associations between annual cardiopulmonary mortality rates and long-term average $PM_{2.5}$ concentrations. While the results of these studies (and their reanalyses) were compelling, they were limited by a lack of detailed health outcome data, individual-level risk factor information and characterization of exposure beyond a metropolitan area average concentration. Further, limited experimental information supported the biological plausibility of the observation. Therefore, despite the relationship shown between long-term exposure to PM and increased death from cardiovascular causes, controversy remained about the association between chronic PM exposure and cardiovascular disease (CVD). Uncertainty persists regarding the mechanisms by which long-term exposure to PM may increase CVD, though hypothesized pathways (not mutually exclusive) involve oxidative stress, inflammation, accelerated atherosclerosis, and altered cardiac autonomic function. Recent $ApoE^{-/-}$ mouse models, employing subchronic and chronic (3 or 6 month) exposures to concentrated ambient $PM_{2.5}$ (CAPs), have shown alterations in vasomotor tone, induced vascular inflammation, and potentiated atherosclerosis through NADPH oxidase dependent pathways. , Exposure to CAPs also induced molecular alterations indicative of cardiovascular disease progression in mice prone to develop atherosclerotic lesions.

Since the 2006 NAAQS review, two additional large cohort studies have added to the available epidemiologic database regarding the relationship between long-term exposure to PM and CVD. A study published in 2007 of 65,893 postmenopausal women in 36 US cities reported hazard ratios for CVD events in relation to air pollutant concentrations at the nearest air monitor; a 24% increase in the risk of CVD event and a 76% increase in risk of CVD-related death were associated with an increase of 10 $\mu g/m^3$ $PM_{2.5}$. In 2008, results of the association between chronic PM exposure, mortality, and coronary heart disease (CHD) were published from a cohort of 66,250 women in the northeastern US; an increase of 10 $\mu g/m^3$ of PM_{10} were associated with a 16% increase in all-cause mortality and a 43% increase in fatal CHD.

In 2004, the EPA funded a new, large-scale prospective cohort study of air pollution and CVD, "MESA Air". This 10-year, multi-city, multi-ethnic study combines state-of-the-art cardiovascular epidemiology with state-of-art exposure assessment. Outcome measurements detect subclinical progression of atherosclerosis, and include coronary artery calcification measured via CT scan and intima-medial thickness measured via ultrasound. The exposure assessment includes spatio-temporal modeling of outdoor air concentrations, participant-specific predictions of pollutant infiltration efficiency, and individual time-location patterns. This research will provide precise estimates of the health risks associated with long-term exposure to air pollution in different regions in the US and within urban areas; stimulate hypotheses regarding possible biologic mechanisms; identify groups especially susceptible to the effects of air pollution exposure; and create opportunities to evaluate the anticipated reduction in health risk resulting from regulatory and voluntary risk reduction actions.

Impact and Outcomes: Although recent epidemiology studies have provided convincing evidence of adverse health effects due to long term exposure to PM, there is little understanding of the pathophysiological processes that underlie these effects. The work described in this poster will enhance the biological plausibility of the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity and mortality**.** Studies with reduced misclassification of exposures and outcomes are also refining the exposure-response relationship. Together these studies will provide important information to the OAR to assist in setting an annual standard that adequately protects human health.

Future Directions: The on-going MESA Air study and other ongoing and future EPA-supported PM research will further delineate biological mechanisms underlying initiation or acceleration of cardiovascular disease by PM. Another important future goal for EPA-supported research will be to understand the sources and components of PM and other pollutants, and how these multiple pollutants interact and impact cardiovascular health.

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Poster # LTG 1-06

What are the Physiological Mechanisms by which PM Affects the Vascular System?

Presenter: Robert D. Brook, MD, University of Michigan, Ann Arbor, MI

Poster Summary: The vascular system coordinates systemic hemodynamics and tissue perfusion. The innermost vessel layer (endothelium) plays a key role in the regulation of vasomotor tone, vascular integrity, coagulation, and thrombosis. Intact endothelial function prevents vascular inflammation and the development of chronic atherosclerosis and hypertension. PM exposure has been shown to impair diverse aspects of systemic and pulmonary vascular function by a range of in vivo animal and human studies. Vascular dysfunction, along with the many associated biological consequences (e.g. increased blood pressure, vasoconstriction), is likely a central mechanism whereby the inhalation of PM instigates acute cardiovascular (CV) events (e.g. myocardial infarctions) and promotes the development of chronic CV diseases (e.g. atherosclerosis). Numerous EPA-funded studies have demonstrated adverse vascular responses following PM exposure and have helped elucidate the underlying biological mechanisms. These experiments demonstrate that PM can affect the systemic vasculature by 2 broad pathways. Particle-induced lung oxidative stress and inflammation have been shown to be transmitted throughout the circulation via increased levels of cellular (e.g. activated leukocytes), humoral (e.g. cytokines), and/or vasoactive (e.g. endothelin) mediators. In conjunction, inhaled PM can interact with lung receptors/nerves and trigger reflex autonomic nervous system (ANS) imbalance favoring sympathetic activity. Physiological responses observed in human panel and chamber studies, along with animal exposure experiments, include PM-induced increased blood pressure, arterial vasoconstriction, impaired endothelial-dependent vasodilatation, and blunted myocardial perfusion. Moreover, longer-term exposures have proven capable of augmenting atherosclerosis in animal models, the relevance of which is supported by several human observations (e.g. increased carotid intima-media thickness). In the context of mechanisms, the studies indicate that PM exposure causes a pro-hypertensive response within minutes via acute autonomic imbalance. Increased circulating (or locally generated) endothelin levels may play a role in the acute vasoconstriction. Several hours-to days later, oxidative stress has been shown to develop within the vasculature, likely as a consequence of a systemic inflammatory response. At the molecular level, oxidative stress is fundamentally involved in the mechanisms related to vascular dysfunction and atherosclerosis. Experiments have shown it to be derived from the up-regulation of cellular sources of reactive oxygen species, including NAD(P)H oxidase and uncoupled endothelial nitric oxide synthase. Products of activated immune cells (e.g. myeloperoxidase) and the autonomic imbalance may also play roles. Among the diverse consequences illustrated are impaired vasodilation (e.g. decreased nitric oxide bioavailability), sensitization of the vasculature to vasoconstrictors and their pathways (e.g. enhanced Rho kinase signaling). These promote vasoconstriction, impaired tissue perfusion, and increased blood pressure. Other consequences include changes in vascular structure and stability (matrix metalloproteinases) that further favor plaque instability.

Impacts and Outcomes: These EPA-funded studies have elucidated the mechanisms of PM-induced vascular dysfunction (and associated physiological responses) and corroborated that it is likely a central pathway underlying the increased CV morbidity/mortality following PM exposure.

Future Outcomes: Future research will focus on determining the PM constituents and sources responsible, identifying the determinants of individual susceptibility, further elucidating the physiological and molecular mechanisms involved, and on identifying potential strategies to prevent or minimize PM-induced vascular effects.

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Poster # LTG 1-07

How does PM affect the nervous system?

Presenter: Mike Kleinman, So. CA PM Center

Poster Summary: Available clinical and experimental evidence lends support to the premise that exposure to ambient particulate matter can affect the nervous system and evidence is accumulating that PM-induced effects in the brain may also mediate cardiopulmonary function, morbidity and CNS disorders. PM-induced dysfunction of the autonomic nervous system may involve direct reflexes from receptors in the lungs and/or to local or systemic inflammatory stimuli and cardiac malfunction due to ischemic responses in the myocardium and/or altered ion-channel functions in myocardial cells. Ultrafine particles are consistently and significantly associated with decreased low-to-high frequency ratio (LF/HF), a measure of sympathovagal balance related to heart rate variability. Histological evidence of neurodegeneration has been reported in both canine and human brains exposed to high ambient PM levels, suggesting the potential for neurotoxic consequences of PM-CNS entry. PM mediated damage may be caused by the oxidative stress pathway. Microscopic examination of coronal sections of the brain, immunocytochemically stained for dopamineric neurons, have indicated that neurons from the substantia nigral nucleus compacta are significantly reduced by 29% in Apo E-/- mice exposed subchronically to concentrated ambient particles (CAPs) relative to air-exposed Apo E-/- controls. Immortalized microglial cells incubated with CAPs evidenced upregulation of genes related to inflammatory pathways associated with Toll-like receptor signaling, MAPK signaling, T- and B-cell receptor signaling, apoptosis, and various proinflammatory cytokines and their receptors. The brains of CAPs-exposed Apo E-/- mice show clear evidence of aberrant immune activation as judged by a dose-related increase in nuclear translocation of two key transcription factors, NF-kappaB and AP-1. These factors are involved in the promotion of inflammation. Increased levels of glial fibrillary acidic protein (GFAP) were also found which is consistent with the in-vitro responses seen in microglial cells. Exposure to concentrated ultrafine particles also enhances TLR-2 mediated responses in the brain of Apo E-/- mice. Consistent with the increased activation of inflammatory pathways, CAPs exposure of mice also induces increased levels of proinflammatory cytokines interleukin-1 alpha (IL-1alpha) and tumor necrosis factor alpha (TNF-alpha) in the brains of exposed mice compared to those of control animals. The mechanism of how PM exposure induces effects in the brain is not yet defined, however, after acute inhalation exposure to ultrafine particles in rats there is evidence that a very small fraction (~0.2%) of the inhaled particles can translocate from the lung to secondary organs including the liver, spleen, brain, and kidneys. For these secondary organs, the peak concentration was found at day 7 after inhalation. Thus, while the mechanism of brain exposure is not fully resolved, there is consistent evidence that exposure to ambient PM can induce inflammatory effects in the brain and that PM-induced CNS effects can, in addition to direct neurotoxicity, can impact cardiopulmonary health.

Impact and Outcomes: Clinical and experimental evidence indicates that exposure to ambient particulate matter can affect the nervous system and PM-induced effects in the brain may mediate degradation of cardiopulmonary function, morbidity and CNS disorders. These studies provide important information to the OAR as it considers whether the current PM standards are protective of all susceptible populations.

Future Directions: Extension of studies to evaluate the potential role of PM exposures as a contributor to degenerative CNS diseases as well as studies of the role of CNS impacts on autonomic control of cardiovascular responses is needed.

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Poster # LTG 1-08

Is Exposure to Ozone Associated with Increased Risk of Human Mortality?

Presenter: Michelle L. Bell, Yale University School of Forestry & Environmental Studies, Yale School of Public Health

Poster Summary: Epidemiological studies over the past several years have added substantial evidence regarding the association between exposure to tropospheric ozone and risk of human mortality. Most studies have focused on short-term exposure (i.e., exposure over the same day and previous few days), overall finding consistent evidence that short-term ozone exposure is associated with higher risk of mortality, especially for cardiovascular or respiratory causes. These include findings from a range of study designs: meta-analyses of previously conducted time-series studies; multi-city time-series studies; and multi-city case-crossover studies. A recent study found long-term ozone exposure to be associated with higher risk of mortality as well, particularly for respiratory causes.

Some research found higher effect estimates during the warmer periods of the year; however this was not consistent across studies. One study found an apparent diminishing effect of ozone's association with mortality through the warm season indicating potential adaptation. Studies examining whether some segments of the population are more susceptible than others have identified older persons (>65 years), African-Americans, women, and those with atrial fibrillation as potentially more vulnerable. Higher health effect estimates were observed in communities with higher rates of unemployment or African-American populations, or lower central air conditioning prevalence. Research findings show no indication of a threshold below which ozone is not linked with increased mortality risk. Many studies investigated PM, often as $_{PM10,}$ as a potential confounder for the ozone and mortality association. Findings suggest that PM is unlikely to be a confounder for the ozone and mortality associations. This robustness remained even at very low ozone levels. However, one study found lower effect estimates with adjustment by sulfate particles, as opposed to PM total mass.

Impacts and Outcome: The studies summarized in this poster provide strong evidence that tropospheric ozone is associated with increased risk of human mortality. The associations are present even at levels well below current health-based National Ambient Air Quality Standards (NAAQS). Higher effect estimates were generally observed for mortality by cardiovascular and respiratory causes.

Future Directions:

Additional research is needed to better understand the susceptible subpopulations. For example, most but not all studies have found higher effects for older age groups. Future research can also investigate the underlying reasons behind increased vulnerability, which may relate to lower baseline health care status, access to medical care, differential exposure patterns, or other factors. Future research may address the specific biological mechanisms through which ozone harms human health, particularly in reference to impacts from both short-term and long-term exposure and to potential susceptibility for those with pre-existing conditions. While findings indicate that effects exist at low levels, most of this work was based in urban areas, and research in rural levels with lower ozone levels could add further insight to impacts at low levels.

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Poster # LTG 1-09

What Novel Approaches are Being Developed and Applied to Improve Exposure Characterization and Risk Estimates of Air Pollution Health Effects?

Presenter: Lisa Baxter, US EPA Office of Research and Development

Poster Summary: Numerous health studies have used measurements from a few central-site ambient monitors to characterize air pollution exposures. Relying on solely on central-site ambient monitors does not account for the spatial–heterogeneity of ambient air pollution patterns, the temporal variability in ambient concentrations, nor the influence of infiltration and indoor sources. Central-site monitoring becomes even more problematic for certain PM components (e.g., metals) or size fractions (e.g, coarse, ultrafine) that exhibit significant spatial-heterogeneity. Improving characterization of air pollution exposures involves novel approaches to estimating ambient concentrations, a better understanding of the personal-ambient relationship, and personal exposure modeling.

Estimates of ambient concentrations have been enhanced by utilizing both measurements and modeling tools. Statistical interpolation techniques and passive monitoring methods can provide additional spatial resolution in ambient concentration estimates. In addition, spatio-temporal models, which integrate GIS data and other factors, such as meteorology, have also been developed to produce more resolved estimates of ambient concentrations. Models, such as the Community Multi-Scale Air Quality (CMAQ) model, estimate ambient concentrations by combining information on meteorology, source emissions, and chemical-fate and transport. In addition, hybrid modeling approaches, which integrate regional scale models (such as CMAQ) with local scale dispersion models, also provides new alternatives for characterizing ambient concentrations. Publically available data on housing characteristics and commuting patterns can be utilized to understand the personal-ambient exposure relationship. The age and size of the home will affect the proportion of personal exposure due to ambient air, and commuting patterns will influence how representative an ambient monitor is to ambient exposure. Since publically available data is limited, estimating personal exposure modeling approaches, such as the Stochastic Human Exposure and Dose Simulation Model (SHEDS), are being developed. The SHEDS model is a population exposure model which calculates average personal exposure using a probabilistic approach to predict the distribution of exposures for the population of interest in various microenvironments. Various exposure characterization approaches are currently being applied and evaluated in several epidemiological investigations.

Impacts and Outcomes: When central site monitoring is used as a surrogate for air pollution exposure it does not take into account the spatial–heterogeneity pattern, particularly for certain PM components and size fractions. This variation may be influenced by meteorology as well as emissions from both regional and local sources. In addition, using central site monitors does not reflect the influence of ventilation or indoor sources. Given that people spend the majority of their time indoors, the infiltration of outdoor air indoors and indoor sources can greatly affect the personal-ambient exposure relationship. Improving air pollution exposure characterization will result in more accurate risk estimates of associated health effects to inform future development of NAAQS and other air pollution regulations.

Future Directions: Improved models of ambient concentrations could be utilized in the reanalysis of existing PM health studies leading to more precise and potentially larger health effect estimates. In addition, studies have observed significant heterogeneity in PM-health effects across locations. One potential reason is that while PM mass concentrations may be similar across locations the composition may be very different making the understanding of sources very important. Another potential reason for the observed variability may be due to the geographic differences in the personal-ambient exposure relationship necessitating a better understanding of personal exposures. Additional model development will occur in estimating personal exposure to PM species and specific sources and in developing an individual specific exposure model for use in cohort health studies.

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Poster # LTG 1-10

How would PM cause adverse health effects through oxidative stress mechanisms?

Presenter: Arthur K. Cho, Southern California Particle Center and Supersite

Poster Summary: A major development in understanding the molecular basis of the adverse effects caused by PM has been the elucidation of the link between oxidative stress and the ability of PM to induce pro-inflammatory effects in target organs. Reactive species in PM participate in chemical reactions that initiate oxidative stress responses by oxidizing or alkylating target cellular protein thiols. The species can be organic or inorganic and are likely to act via two mechanisms: oxidation of thiols by ROS generated by redox reactions in which reactive chemical species act as catalysts; and a reaction involving an electrophilic reactive center in PM which forms covalent bonds with thiols, thereby inactivating the thiol function or depleting thiols in general. When thiols on regulatory proteins are altered by redox or electrophilic reactions, downstream cell signaling pathways are affected, resulting in pathophysiological reactions such as inflammation. PM is a complex mixture that includes organic compounds and metal, both of which are capable of inducing ROS formation. The concentrations of quinones found in PM have been measured in multiple diesel exhaust and ambient air samples and generally follow the concentration of PAHs which are converted to quinones by combustion, photochemical oxidation and biotransformation. Assays have been developed to measure oxidants, Fenton reaction cataylsis, electron transfer catalysis, and the presence of electrophiles. Application of these assays to PM samples from multiple sources have demonstrated correlations between the concentrations of quinones and redox and electrophilic activity as well as the capacity of the sample to induce the stress protein HO-1 in cells, indicating that the capacity of a given sample to induce a state of oxidative stress can be predicted from these assays. These assays also correlate with inflammatory cellular responses involved in asthma and in atherosclerosis. A mouse intranasal sensitization model was used to demonstrate ultrafine PM had higher redox activity and caused enhanced sensitization, leading to eosinophilic inflammation and mucoid hyperplasia, as compared with fine PM. Some of these effects could be partially suppressed by N-acetyl cysteine, a cellular thiol enhancing agent, consistent with the notion that thiol oxidation or modification is a key step in the adverse effects of PM. Instillation of PM into rats increased inflammatory markers in bronchoalveolar lavage fluid and these effects were inhibited by prior administration of an SOD analog, supporting the notion that PM-induced pulmonary inflammatory responses are mediated by ROS. Exposure of rats to fine CAPS caused increased oxidative stress in the heart and altered cardiac function that was ameliorated with the vanillin receptor antagonist, capsazepine. This receptor can potentially affect downstream cell signaling pathways. Cultured epithelial cells exposed to nanodiamonds, hitherto thought of as biologically inert, produced increased expression IL-8 in association with oxidative stress. In summary, chemical species associated with PM have the capacity to generate ROS or form covalent bonds with thiols. Both of these reactions increase the expression of stress proteins as well as inflammatory cytokines involved in observed pulmonary and cardiovascular changes in animal models.

Impacts and Outcomes: Assays designed to characterize the ability of PM to induce oxidative stress have been shown to predict the in vitro and in vivo responses to various PM. Oxidative stress appears to be an important underlying mechanism by which PM causes adverse health effects. This approach has the potential to allow the EPA to group multiple PM components or sources by their mode of action, which will provide important information as to the EPA as it considers potential strategies to regulate specific PM components or sources.

Future Directions: Future studies will address the selectivity of redox and electrophilicity in activating downstream cell signaling pathways involved in the PM-induced pathological events.

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Poster # LTG 1-11

What Are the Cellular and Molecular Mechanisms by Which PM Causes Adverse Health Effects?

Presenter: James M. Samet, US EPA Office of Research and Development

Poster Summary: Epidemiological and toxicological studies have implicated respiratory and cardiovascular inflammatory responses in the pathophysiological effects of PM exposure. Inflammatory responses are mediated by key inflammatory proteins whose transcriptional expression is under the control of signal transduction pathways that transmit extracellular signals to the cytoplasm and nucleus depending on the state of phosphorylation of key intermediate proteins. The extent of protein phosphorylation in the cell is the net result of the opposing activities of specific kinases and phosphatases. Therefore, the relative kinase and phosphatase activities are vital indicators of this activation, and can be inferred from the extent of phosphorylation of specific intracellular proteins. The data presented here is representative of studies that have focused on the molecular mechanisms through which PM components induce signal transduction in the cell following exposure to diesel exhaust particles (DEP), the ubiquitous PM metal Zn^{2+}, or organic constituents of ambient PM (OC), including quinones and vapor phase samples. These studies have shown that pivotal signaling kinases, such as the Epidermal Growth Factor Receptor (EGFR) can be activated by exposure to non-cytotoxic concentrations of DEP, OC or Zn^{2+}, resulting in the phosphorylation-dependent activation of signaling cascades that are linked to the expression of inflammatory mediators. The mechanism responsible for DEP- , OC- and Zn^{2+}-dependent signaling activation appears to be, showing ligand-independent activation of EGFR that occurs through inhibition of phosphatase activity. These studies elucidate a molecular mechanism involving the disregulation of phosphoprotein metabolism that leads to inappropriate signal transduction activation following exposure to PM.

Impact and Outcomes: The toxicological effects of ambient PM are the result of cellular responses to exposure to PM component such as DEP. Elucidation of the cellular and molecular mechanisms through which these adverse effects occur will:
1) Provide biological plausibility in furtherance of our understanding of the health effects of PM,
2) Produce potential biomarkers of exposure and effect,
3) Aid in the identification of hazardous PM components and, thereby, facilitate the targeting of regulatory efforts aimed at mitigating the adverse effects of PM.

Future Directions: 1) Develop imaging approaches amenable to computational modeling of the activation of pivotal signaling events initiated by PM exposure,
2) Provide in vivo validation of the toxicological relevance of PM effects in vitro,
3) Further link signaling pathways activated by PM components to specific adverse outcomes such as inflammatory mediator expression and identify responsible physicochemical properties in PM.

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Poster # LTG 1-12

How Does Pre-Existing Cardiovascular Disease Set The Stage For Sensitivity To PM?

Presenter: Aimen K. Farraj, US EPA Office of Research and Development

Poster Summary: Day-to-day variations in airborne particulate matter (PM) associated with air pollution have been linked to increases in morbidity and mortality, especially in individuals who have pre-existing cardiovascular (CV) disease. Several mechanisms of PM-induced cardiac dysfunction in humans have been postulated including autonomic modulation, direct effects of PM constituents on ion channels, myocardial ischemia, and vascular dysfunction related to systemic inflammation. Data generated from the U.S. EPA's PM research program includes several recent advances in the understanding of how pre-existing CV disease confers enhanced sensitivity to the effects of PM inhalation. These include epidemiological, controlled clinical and toxicological *in vivo*, *ex vivo*, and *in vitro* studies. Recent epidemiological studies provide further evidence that cardiovascular disease heightens sensitivity to PM exposure including the findings that PM exposure increased mortality risk in heart failure patients (Medina-Ramon et al, 2008), and increased the risk of cardiac arrhythmias in individuals with coronary heart disease (Berger et al, 2006). These findings in humans are supported by recent findings in animal models. PM exposure caused an augmentation of effects in ischemic animals (Cozzi et al, 2006), vascular disease progression in atherosclerotic mice (Floyd et al, 2009), exacerbated pathophysiology in hyper-lipidemic rabbits (LaGier et al, 2008), greater pulmonary edema and injury in stroke-prone rats (Wallenborn et al, 2007) and autonomic dysregulation (Elder et al, 2007) and increased cardiac arrhythmias (Farraj et al, 2009) in hypertensive rats. There have been breakthroughs in the understanding of the mechanisms of these effects. Recent epidemiological findings point to a potential role of systemic inflammation (Delfino et al, 2008; Dubowsky et al, 2006; Ruckerl et al, 2007), platelet activation (Delfino et al, 2008; Ruckerl et al, 2007), and reduced antioxidant status (Delfino et al, 2008) in PM-induced exacerbation of coronary artery disease. Animal studies have provided mechanistic insight as well. Exposure to PM exacerbated myocardial ischemia (Bartoli et al, 2009a) and elevated blood pressure (Bartoli et al, 2009b) by increasing vascular resistance in dogs, altered hemostasis in mice (Cozzi et al, 2007), induced a hypertensive-like cardiac gene expression pattern in rats (Gottipolu et al, 2009), and increased plasma renin-angiotensinogen, blood coagulation factors and fibrinolysis in hypertensive rats (Upadhyay et al, 2008).

Impacts and Outcomes: According to the American Heart Association, 35 % of all deaths (close to 900 K) in 2005 were due to CV disease in the U.S. and greater than 36 % of all adults (80 million people) suffered from CV disease in 2006. The pronounced adverse effects of particulate pollution in individuals with CV disease are thus a major public health problem. An increased understanding of these effects will encourage the discussion of susceptibility as a factor in the standard-setting process, provide critical support for regulatory policy for PM by the US EPA, and potentially lead to improvements in public health by decreasing morbidity and mortality associated with PM exposure.

Future Directions: Although several mechanisms of PM effect have been postulated, they are not mutually exclusive and very likely operate concurrently. Some of the factors that may influence the predominance of a specific mechanism and thus should be further studied include the type and severity of CV disease, the systemic translocation of particles, lung disease co-morbidity, the propensity for inflammatory responses in diseased individuals, and the impact of the physicochemical characteristics of PM. Finally, it will be necessary to further develop animal models to better reflect the pathophysiologic deficits observed in humans with CV disease and to enable further progress in the understanding of the mechanisms by which CV disease confers enhanced sensitivity to the adverse effects of PM.

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Poster # LTG 1-13

Does Particulate Matter Cause or Exacerbate Asthma?

Presenter: David Peden, Center for Environmental Medicine, Asthma & Lung Biology, UNC School of Medicine Chapel Hill, NC

Poster Summary: Asthmatics and children in particular, appear to be more sensitive to PM and other air pollutants than healthy individuals, and thus represent a susceptible sub-population. Epidemiologic, human controlled exposure studies, animal toxicological and cell culture studies are employed in an integrated manner to investigate PM health effects on asthmatics. Studies have shown convincingly that during episodes of air pollution, emergency room visits and medication use in asthmatics increase. Recent studies supported by EPA have also suggested that exposure to combustion related particles such as diesel exhaust and secondary atmospheric products like ozone can increase the actual incidence of asthma events in adults and in children. Animal studies have provided supporting evidence by demonstrating that exposure to various gases or PM results in increased allergic sensitization and subsequent development of allergic lung disease. Endotoxin and other bioaerosols are components of coarse PM which impact asthma as demonstrated in more limited human exposure studies and experimental animal systems. Epidemiology and exposure assessment studies provide information on what type and concentrations of pollutants are in the air, what sources they come from, and whether they are associated with the incidence or severity of asthma in the population. Some recent panel studies have reported that coarse PM elicits more responses in asthmatics than fine PM and, somewhat, surprisingly, more cardiovascular changes than respiratory tract changes. Efforts are also evaluating whether proximity to roadways and mobile sources play a role in the development of allergies and asthma in children. Since people respond differently to the same environmental exposures due in large part to genetic heterogeneity, studies are also underway to better understand genetic and epigenetic factors that contribute to the response of an asthmatic to air pollutants.

Impact and Outcomes: Incidence of asthma in the US has been increasing over the past 30 years. Since the Clean Air Act mandates that EPA set standards to protect susceptible subpopulations, it is important to understand the contributions of air pollution to asthma incidence and exacerbation. The results of these studies are being used in the ISA for PM and by OAR in both benefits assessment efforts and in developing new educational materials and programs to support health messages for the Air Quality Index.

Future Directions: Future Directions in this area call for: developing new biomarkers of risk and exposure in asthmatics using cutting edge molecular genetics approaches; developing a better understanding of differences in airway physiology between asthmatics and healthy people, as they relate to air pollution; identifying mechanisms which underlie the response of asthmatics to PM, determining whether neighborhood differences in air pollutants, proximity to roadways, and mobile sources play a role in the development of allergies and asthma; and identifying potential intervention strategies to better protect asthmatics from PM.

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Poster # LTG 1-14

How Does PM Affect People With Diabetes?

Presenter: Mark W. Frampton, University of Rochester Medical Center, Rochester, NY

Poster Summary: Diabetics have an increased mortality risk from exposure to particulate matter (PM), and double the risk of non-diabetics for a cardiovascular hospitalization related to PM_{10} exposure. Determining the biological mechanisms involved may provide approaches for decreasing cardiovascular morbidity and mortality. EPA-funded research provides new evidence indicating that, in diabetics, PM exposure reduces heart rate variability, increases systemic inflammation, and worsens vascular injury, endothelial dysfunction, and blood coagulation. The association between PM exposure and reduced heart-rate variability was stronger in people with diabetes (1). C-reactive protein, a blood measure of systemic inflammation, increased in association with $PM_{2.5}$ exposure in elderly diabetic nursing home residents in St. Louis (2). Increased exposure to ambient levels of black carbon was associated with increased plasma levels of a vascular adhesion molecule in 92 people with diabetes in Boston (3). The association between PM exposure and increases in white blood cell count was greater in people with the metabolic syndrome (4), a precursor of diabetes that now afflicts 23-24% of the U.S. population. Panel studies of people with diabetes have shown relationships between PM exposure and reduced endothelial function (5) and increased markers of blood coagulation (10). A human clinical study (6) showed that inhalation of laboratory-generated elemental carbon ultrafine particles for 2 hours increased markers of platelet activation and endothelial injury. In a mouse model of obesity and diabetes, acute exposures to concentrated ambient ultrafine particles or freshly-emitted engine exhaust did not significantly increase lung or systemic inflammation or oxidative stress (7, 8). However, in C57BL/6 mice fed a high fat diet, 24 weeks of exposure to ambient concentrated $PM_{2.5}$ increased visceral adiposity, and caused insulin resistance, vascular dysfunction, and systemic inflammation (9). These findings provide plausible mechanistic pathways by which PM exposure increases cardiovascular risk in diabetes.

Impacts and Outcomes: The U.S. is experiencing an epidemic of type 2 diabetes and its associated conditions, obesity and the metabolic syndrome. In 2007 it is estimated that 26% of U.S. adults had abnormal fasting glucose levels, or pre-diabetes. Thus the at-risk population is increasing, and will continue to increase in coming years. Understanding the effects and mechanisms of PM exposure in diabetes is necessary to establish protective air quality standards to minimize risk to susceptible populations. This research is a high priority need identified by the National Institutes of Health**,** the EPA, and the National Academy of Sciences.

Future Directions: Future research needs to: 1) determine the key PM constituents and characteristics responsible for effects in diabetes, 2) determine the mechanisms responsible for systemic inflammatory and vascular effects, 3) identify signaling pathways mediating these effects, 4) investigate PM effects on obesity and insulin resistance, and 5) understand the role of long-term PM exposure in people with diabetes.

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Poster # LTG 1-15

How do genetic or epigenetic factors modify the response of individuals to PM and other air pollutants?

Presenter: Joel Schwartz, Harvard PM Center

Poster Summary: Particulate air pollution results in early deaths, notably from cardiovascular disease. There is considerable interest in understanding the mechanism of these associations, and the relative role of different components of PM. If a particular mechanistic pathway is important, then one might expect polymorphisms along that pathway to modify the effects of exposure. In addition, epigenetic control of gene expression is now recognized as key in many disease processes and could represent an early response to air pollution, or modify the response. Recent research has examined these questions, particularly with respect to metals. Ghio has shown that DMT1 knockout animals have greater inflammatory response to metal rich particles, suggesting that cellular uptake in the lung is a protective mechanism. Consistent with this, human studies have shown HFE polymorphisms (also related to metal uptake) modify the effects of particles on heart rate variability and homocysteine. In addition, occupational exposure to metal rich particles has been shown to chronically produce global hypomethylation, and acutely reduce iNOS methylation, the latter suggesting increased oxidative stress in the endothelium. ROFA and V exposure has been shown to perturb gene expression related to endothelial cells permeability in a toxicologic study using expression arrays, supporting this result. Zn exposure in animals also downregulates mitochondrial function and increases kinase expression. Oxidative stress is a key pathway, with animal studies demonstrating that particles and ozone produce oxidative stress, and human studies demonstrating that genes related to oxidative defenses modify the effects of particles and ozone on heart rate variability, lung function, and endothelial function. Other studies implicate angiotensin II pathways in blood pressure response. Genes related to methyl metabolism also modify the response to particles, suggesting that DNA methylation may be on the causal pathway. Supporting this, traffic particles have been shown to lower global DNA methylation in humans, and Diesel exhaust to downregulate HDAC expression. Lower DNA methylation, in turn, has been shown to be predictive of heart attacks, stroke, and death on follow-up.

Poster # LTG 1-16

How ORD Air Research Supports OAR's Reviews of the National Ambient Air Quality Standards (NAAQS)

Presenters: Beth M. Hassett-Sipple, US EPA Office of Air Quality Planning and Standards, Office of Air and Radiation
Lindsay Wichers Stanek, US EPA National Center for Environmental Assessment, Office of Research and Development

Poster Summary: This poster addresses two basic questions about the NAAQS reviews: 1- How are the NAAQS developed; and 2- How does ORD research contribute to this process?
As required by the Clean Air Act, the EPA sets and periodically reviews primary (health-based) and secondary (welfare-based) NAAQS. The current review process includes four key elements:

- ***Planning –*** An initial public workshop with internal and external scientists provides an opportunity to broadly discuss the key policy-relevant issues around which EPA would structure the specific NAAQS review and to discuss the most meaningful new science that would be available to inform our understanding of these issues. The workshop discussions are used to develop an Integrated Review Plan (IRP) identifying policy-relevant issues and questions to frame the science, risk/exposure, and policy assessments.
- ***Integrated Science Assessment (ISA)*** – A concise synthesis of the most policy-relevant science including key scientific judgments to support risk/exposure assessments as well as evidence-based considerations.
- ***Risk/Exposure Assessment*** (REA) – A concise presentation of quantitative and qualitative estimates of the risks and/or exposures of adverse health and welfare-related effects associated with recent ambient levels, with ambient levels simulated to just meet the current standards, and/or with ambient levels simulated to just meet alternative standards that may be considered.
- ***Policy Assessment/Rulemaking*** – The Policy Assessment Document (PAD) integrates information from the final ISA and final REA to present the scientific basis for framing alternative policy options for consideration by senior Agency management prior to rulemaking. Proposed and final rulemaking notices will address any modifications, as appropriate, to the four elements of the NAAQS including the indicator, averaging time, form, and level.

ORD scientists and grantees conduct critical research that is evaluated and integrated within the broader scientific body of evidence by ORD's National Center for Environmental Assessment (NCEA) in the ISA. ORD scientists also provide important technical consultation and review in the development of the REA, PAD, and rulemaking process.
Future Directions: ORD will continue to develop and refine concise, policy-relevant ISAs with the particulate matter (PM) assessment to be issued in final form by the end of 2009 and the assessment for carbon monoxide (CO) in final form early in 2010. ORD and OAR continue to use the NAAQS review process to inform planning and funding of critical intramural and extramural research for health and welfare effects, monitoring methods development, and numerical model development and evaluation.

Poster # LTG 1-17

Enhancing Scientific Interaction and Communication Between ORD and OAR for Ambient Air Quality Monitoring and Human Health Risk Research

Presenter: Beth M. Hassett-Sipple, US EPA Office of Air Quality Planning and Standards, Office of Air and Radiation

Poster Summary: Air pollution continues to have adverse impacts on human health and the environment in the U.S., despite clear evidence that overall air quality has improved. To understand the relationships between air pollutants and adverse health and welfare effects, researchers utilize ambient air measurement data collected through monitoring networks operated almost exclusively by State, local and Tribal air monitoring programs. However, because ambient air monitoring networks do not capture data everywhere or in some cases every day (e.g., EPA's Chemical Speciation Network typically operates every third or sixth day), there remain important uncertainties especially relating to lag-times and other temporal issues with PM-associated outcomes as well as PM component and co-pollutant attributions.
In April 2008, EPA's ORD and OAQPS co-sponsored a workshop to discuss health research priorities for ambient air quality data that would most advance our understanding of the impacts of criteria air pollutant exposures, with a focus on particulate matter (PM). This workshop built upon an earlier meeting co-sponsored by the Health Effects Institute (HEI) and EPA in late 2006 and upon follow-up discussions with the EPA-PM Center Directors, HEI National Particle Component Toxicity (NPACT) Directors, and other researchers. In particular, EPA sought advice on concrete steps that could be taken to prioritize monitoring sites and/or specific fine particle components for more frequent monitoring in order to facilitate current and future health effects studies and improve comparisons of risk estimates across studies.

Impacts and Outcomes. The workshops served to foster better communication and to facilitate scientific interaction within the air pollution community to gain better and clearer access to relevant data, provide input in monitoring network design, and to develop strategies to begin to acquire the data needed to move forward our understanding of the potential health impacts of criteria pollutants and the relative importance of associated components in the air pollution mix. This poster will summarize specific recommendations for concrete steps that EPA and other organizations could take in the ambient air monitoring program to advance health research for the criteria and related air pollutants as well as assess progress made to date to respond to these recommendations.

Future Directions. The impetus for these workshops has been the growing recognition that current and future changes to the air quality monitoring system could significantly affect ongoing and future epidemiology research. This research serves as a foundation for EPA's reviews of the national ambient air quality standards (NAAQS). Yet resources at the Federal and State/local/Tribal levels for air pollution monitoring continue to diminish, while increasing demands tied to various aspects of NAAQS compliance continue to grow.

Poster # LTG 1-18

ORD Air Pollution Research Spurs Action to Protect Public Health

Presenter: Susan Lyon Stone, US EPA Office of Air Quality Planning and Standards, Office of Air and Radiation

Poster Summary: ORD's research findings have shown that exposure to air pollutants are linked to a range of adverse health effects including premature death from heart and lung diseases, aggravation of heart and lung diseases, hospital admissions, increased medication use and increased susceptibility to respiratory infection. The Office of Air and Radiation, the medical community and other government agencies are taking public health action as a result of these compelling research findings on the health effects of airborne particulate matter (PM) and ozone.
The medical community, through its professional societies: the American Academy of Pediatrics; the American Lung Association; and the American Heart Association; have all issued statements to their membership encouraging physicians to communicate the risks of air pollutants to patients, policymakers and clinicians.

To help the public determine when air pollution risks may be highest, ORD scientists have worked with EPA's Office of Air and Radiation (OAR) in its development of the Air Quality Index (AQI). The AQI is an index for reporting daily air quality. It tells how clean or polluted the air is, and what associated health effects might be a concern, especially within a few hours or days after exposure.

OAR has used research and clinical information from ORD to develop high-quality information materials for the public and media. In addition to a medical poster and fact sheets to help communicate this, OAR has used information from ORD research to develop a Web course for healthcare providers about ozone and their patients' health. A Web course for healthcare providers about PM and their patients' health is nearing completion.

To reach people at greatest risk, a program called "EnviroFlash" is currently available in 37 states to provide air quality data to people via cell phone, pager or e-mail so they can plan their day and protect their health. "AirCompare" is a Web site that allows people to compare air quality in different locations, or in one location for different months of the year, to inform decisions about vacation or relocation.

Information about the health effects of PM have been especially useful in developing tools to protect public health during smoke events. This information was utilized in the development of the Wildfire Guide for Public Health Officials, a collaborative effort between EPA, the California Department of Public health and Air Resources Board, and the Missoula County Health Department. New research by ORD is expected to play a key role in responding to the public health threats from biomass burning.

Impacts and Outcomes: As ORD continues improving its ability to predict air quality and understand the health consequences of exposure to air pollutants under different conditions, that information will help public health agencies to reach those most at risk and help prevent or reduce illness and deaths from respiratory and cardiovascular disease.

Future Directions: EPA is working with other agencies to expand public health outreach. One example is working with the Centers for Disease Control and Prevention (CDC) in the development of a National Environmental Public Health Tracking Network (NEPHTN). With the public's expanding interest in serious health effects associated with ozone and PM, public health officials are looking for better ways to use the available air quality data to develop information for use in the NEPHTN. OAR and ORD, together with CDC conducted a pilot study to develop integrated, geo-coded, air quality data sets from routinely available sources for specific use by public health officials. Collaboration with the National Aeronautic and Space Agency, and the National Oceanic and Atmospheric Administration is a key component to developing the air quality data base.

Relevant Publications

American Lung Association http://www.lungusa.org/ Air Quality, 2008 State of the Air

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U.S. Centers for Disease Control and Prevention 2005: http://www.cdc.gov/nceh/tracking/tracking_network_workgroups_report.htm

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U.S. Environmental Protection Agency (2005) Air quality criteria for ozone and related photochemical oxidants (first external review draft). Research Triangle Park, NC: National Center fir Environmental Assessment; report no. EPA/600/R-05/004aA-cA. Available: http://cfpub.epa.gov/ncea..

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Poster Contributors:

Office of Air and Radiation: S. Jackson, D. Mintz

Office of Research and Development: F. Dimmick, J. Szykman

Poster # LTG 1-19

Health Effects Institute: A Unique Model of Public-Private Partnership

Presenter: Rashid Shaikh, Ph.D., Director of Science, Health Effects Institute, Boston, MA

What is HEI: The Health Effects Institute is an independent nonprofit organization, chartered to conduct and evaluate research related to the health effects of emissions from motor vehicles and other sources in the environment in order to inform decisions in the public and private sectors. The Institute provides decision makers with independent, impartial, timely, and high quality scientific information on the health effects of emissions from motor vehicles, fuels, and other sources of environmental pollution.

Funding: Typically, HEI receives half of its core funds from the US Environmental Protection Agency and half from the worldwide motor vehicle industry. HEI has leveraged its core sponsorship base to include domestic and international sponsors from a range of government, industry and foundation sponsors in Europe, Asia and Latin America.

What does HEI do? To accomplish its mission, HEI (i) identifies the highest priority areas for health effects research; (ii) funds and oversees the conduct of research in such areas; (iii) provides comprehensive, independent review of HEI-supported and related research; (iv) integrates HEI's research results with those of other institutions into broader evaluations; and (v) Communicates the results of HEI research and analyses to public and private decision makers.

Governance: HEI's independent Board of Directors consists of leaders in science and policy committed to the public-private partnership that is central to the Institute. The Health Research Committee works with scientific staff to develop a *Five-Year Strategic Plan for Understanding the Health Effects of Air Pollution* with input from HEI's sponsors and other interested parties, develops specific research requests, selects meritorious research projects for funding, and oversees their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

HEI Research Priorities:

- Air Pollution Mixture, including research on PM, gases, and air toxics, such as studies on better exposure characterization, studies on indoor, outdoor and personal exposure to PM and gases, mechanism on cardiovascular toxicity, PM and asthma, mechanism of action of butadiene and acrolein, and studies in potential 'hot spots.' HEI is in the midst of a major study focused on toxicity of different components of PM (NPACT) and HEI has recently published a extensive review of the literature on traffic related exposures.
- Emerging Technologies and Fuels, including the Advanced Collaborative Emissions Study (ACES) to characterize emissions and test health effects of 2007 and 2010 diesel engines.
- Assessing the Public Health Impact of Air Quality Actions (Accountability) including an assessment of short- or long-term regulatory actions and changes in public health.
- Enhanced International Perspective, including a modest program of research and capacity- building in China, Hong Kong, Vietnam, South America and India.

During its 30 year history, HEI has funded about 300 studies in North America, Europe, and Asia, and published over 200 research and special reports, providing important information to inform decisions on carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants.

Recent HEI Publications

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- Zeger SL, McDermott A, Dominici F, Peng R, Samet J. 2006. Internet-Based Health and Air Pollution Surveillance System. Communication 12. Health Effects Institute, Boston, MA. 2006